PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Improvements in or relating to Veterinary Compositions for Treating Mastitis

We, ASTRA-HEWLETT LIMITED, a British Company, of King George's Avenue, Watford, Hertfordshire, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to veterinary compositions, and in particular to compositions useful in the treatment of mastitis and related infections.

The use of compositions comprising antibiotics in treating mastitis is well known, the compositions being introduced into the cow's udder. Such compositions comprise the antibiotic in an oily base of high viscosity, which may be of mineral or vegetable origin. For example, the base may comprise a mineral oil whose viscosity has been increased by gelling with a small amount of an aluminium soap, usually aluminium monostearate, or it may comprise a vegetable oil such as arachis oil thickened with Beeswax or theobroma oil.

Compositions intended for the purpose must maintain an antibiotic concentration in the udder for a period of time sufficient to eliminate the mastitis organisms completely. On the other hand, it is undesirable that antibiotics should be present for longer than is required for this purpose, since if they are, either healthy milk must be discarded or milk containing quite a substantial proportion of the antibiotic comes on the market.

It is also important that the compositions used have suitable viscosities both at ambient temperatures, at which they will normally be kept and at which they will be administered, and also at the body temperature of the cow, about 37° C. in addition the compositions must be stable during storage; that is to say, the antibiotic must not separate out to any substantial degree, neither must oil seep from the collapsible metal tubes in which this type of preparation is usually packed.

In the past it has been found, generally speaking, that compositions whose viscosity properties and stability are satisfactory from the standpoint of storage and administration tend to release the antibiotic very slowly and thus allow substantial amounts to be found in the milk for a number of days after the elimination of the mastitis infection. Additionally there is a great variation in the rate of release of antibiotic from such preparations even when they are of identical composition, because slight differences in the method of preparation of the gel cause great differences in the viscosity and other physical properties of the gel, which in turn greatly influence the rate of release of the antibiotic.

It has now been found that the rate of release of antibiotics from compositions of the type described can be increased in a readily controllable manner by incorporating in the composition a finely divided water-soluble compound which by itself is substantially without therapeutic action in the concentration in which it will in use be contained in the milk.

In its broadest aspect the invention comprises compositions comprising a therapeutic agent in a hydrophobic viscous or gel base, and comprising in addition at least 10% by weight of a solid, finely divided physiologically innocuous non-gelling water-soluble compound of average particle size below 150 microns.

More particularly the invention comprises compositions suitable for use in the treatment of mastitis and related infections in animals, which comprise an antibiotic, a hydrophobic

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viscous or gel base, and in addition at least 10% by weight of a solid, finely divided physiologically innocuous non-gelling water-soluble compound which, in the concentration in which it will be contained in the milk, is substantially without therapeutic action in the said infections.

The actual solubility of the water-soluble substance is not critical, provided that it has a slight solubility at 37° C. in the milk. The lower limit of solubility is about 0.1% by weight at 37° C. in milk and there is no upper limit of solubility. Very soluble and very sparingly soluble substances alike can be used.

It is important that the additional water-soluble compound should be finely divided, since if it is not it has no useful effect on the rate at which the antibiotic is released. It should in practice have a maximum particle size below 50 microns and preferably below about 20 microns, the average particle size preferably being about 10—20 microns or even less.

The additional water-soluble substance may be organic or inorganic in nature. Its effect on the rate of release of the antibiotic is believed to be the result of a purely physical mechanism, and its chemical nature is unimportant, provided of course it has not untoward physiological effects. Finely ground sodium chloride is very suitable, and has the advantages of being both cheap and a physiological substance. Finely ground sucrose (e.g. icing sugar) or other sugars such as lactose and dextrose are also suitable materials. Calcium lactate is useful, and also is a normal constituent of milk. It will, however, be apparent that a great number of compounds have the properties required, and that while those mentioned above may be regarded as particularly good practical examples, they are no more than examples.

The proportion of the additional water-soluble compound will vary with the other characteristics of the composition, for example its viscosity (which itself will be affected thereby), and also with the rate of release desired. Generally it will be between 10 and 66% and especially between 25 and 50%, of the weight of the final composition. It should not of course be such as to increase the viscosity of the composition to a level at which it is difficult to administer, but subject to this proviso the presence of the additional water-soluble substance does make it possible to use compositions of higher viscosity than would be satisfactory in its absence.

It is an important advantage of the invention that by a simple adjustment of the proportion of the additional water-soluble substance, the other characteristics of the composition remaining unchanged, it is possible to adjust the average time of release, so that compositions adapted to various situations and requirements are readily made, and can be labelled in accordance with their rates of release. It will, however, be understood that such labelling can only be average and approximate, since as is well known the actual rate at which the antibiotic is released always varies to some extent from cow to cow, and even from quarter to quarter of the same cow. Nevertheless, the time of release, i.e. the time for which appreciable quantities of antibiotics will be present in the milk, can be predicted and indicated for the majority of beasts with sufficient accuracy for practical purposes.

The other constituents of the composition may be conventional. Thus the antibiotic may be a penicillin or a streptomycin that is known to be active against mastitis organisms, the latter being useful particularly when penicillin-resistant organisms are encountered. Examples include benzyl-penicillin, procaine-penicillin, streptomycin and dihydrostreptomycin sulphate. If desired, the compositions may contain also another therapeutic agent, e.g. a sulphonamide such as sulphadimidine. The antibiotic and any other therapeutic agent are normally in a finely divided form, e.g. of particle size below about 40 microns.

As the hydrophobic base it is preferred to use a mineral oil, e.g. medicinal paraffin, gelled with an aluminium soap which will usually be aluminium monostearate; the pure aluminium monostearate need not be used, commercial aluminium stearate, which contains free alumina and free stearic acid, being quite satisfactory. The amount of aluminium mono-stearate in the base depends on the particular mineral oil used and on the viscosity properties desired, but is usually about 3% by weight in known practice; if, however, higher viscosities are desired, such as can be obtained for example by using a higher proportion of aluminium mono-stearate, the present invention makes it possible to use them while keeping the rate of release at an acceptable level.

While the above bases have their advantages, the invention can be applied also to compositions in which other base materials of either mineral or vegetable origin are used, e.g. arachis oil thickened with Beeswax, or theobroma oil, or mixtures of soft paraffin and/or hard paraffin and a mineral oil such as medicinal paraffin.

The compositions of the invention can be made up in the conventional way, i.e. in collapsible metal tubes holding a dose of about 100,000 i.u. of antibiotic.

The invention is illustrated by the following Examples. All percentages are by weight. In all the Examples the penicillin in the milk was estimated by plate assay using *B. subtilis* for the first milk samples after treatment and until the levels of penicillin in the milk had fallen to 0.1 i.u./ml. After this a tube assay using the triphenyltetrazolium chloride method and *Str. thermophilus* was employed to detect

lower levels of penicillin and other antibiotics in the milk down to a level of 0.05—0.01 i.u./ml. (penicillin equivalent). The aluminium mono-stearate used was the commercial product.

EXAMPLE 1

Three preparations were made using a base comprising 85% of liquid (medicinal) paraffin and 15% "Cosmogel" (soft paraffin), the base being gelled by the incorporation of 3% aluminium monostearate followed by a conventional heat treatment.

For one preparation, sodium benzyl-penicillin was added to the base described so that 100,000 i.u. were contained in a dose (about 4 grams).

For a second preparation, 3 parts by weight of the base were mixed with 1 part by weight of finely powdered sodium chloride ground to an average particle size of 10—20 microns; the powder contained some finer particles and some larger ones up to a maximum size of about 40 microns. Sodium benzyl-penicillin was also added to this preparation so that 100,000 i.u. were contained in a dose of about 4 grams as before.

For the third preparation, 3 parts of the base were taken and mixed with 1 part of finely ground sucrose (icing sugar). Again the average particle size of the powder was 10—20 microns. Penicillin was also added so that 100,000 units were contained in a dose of about 4 grams.

Three groups of cows were treated, one group with each preparation. Each cow received one dose per quarter of the udder, i.e. 4 doses per cow (approximately 400,000 i.u. penicillin per udder) of the appropriate preparation. The milk from each cow was collected separately at each milking (every 12 hours) subsequently and was assayed for penicillin.

After 36 hours milk from the group which received the plain base preparation still contained on average 1.0 i.u./ml. of penicillin; at 72 hours it contained on average 0.15 i.u./ml. The milk from no cow in this group was substantially free from penicillin (i.e. contained less than 0.05 i.u./ml.) until 96 hours after treatment, and 120 hours were required before all cows were substantially clear.

In the group receiving the same dose of penicillin in the same base but with the inclusion of 25% of finely powdered salt, the average level of penicillin in the milk was 0.2 i.u./ml. at 36 hours. 60% of the group were free of penicillin in the milk at 48 hours and all cows were clear at 60 hours.

In the group receiving the preparation containing 25% of finely powdered sugar, the average penicillin level in the milk was 0.55 i.u./ml. at 36 hours. At 60 hours one cow had no significant penicillin in the milk, the average level in the other 4 cows being then 0.1 i.u./ml. At 72 hours, 3 cows were free of penicillin and at 84 hours all cows were clear.

The Example illustrates the beneficial effect of a finely powdered water-soluble substance, whether this be organic or inorganic, on release time when incorporated with benzyl-penicillin in a mineral oil-aluminium monostearate gel base.

EXAMPLE 2

A similar experiment as in Example 1 was carried out, using a base comprising arachis oil thickened by the inclusion of 15% of white Beeswax.

Preparations with 100,000 i.u. penicillin per dose were made as before, using a mixture of 3 parts by weight of the base and 1 part by weight of finely powdered sodium chloride.

Two groups of cows were treated with these preparations in the same manner as in Example 1.

At 36 hours cows receiving the plain base preparation plus penicillin showed an average level of 2.0 i.u./ml. penicillin in the milk; at 72 hours the level was 0.4 i.u./ml. One cow in the group was clear (less than 0.05 i.u./ml. in the milk) at 84 hours but in the other 4 cows penicillin persisted in the milk for more than 120 hours.

The average penicillin level in the group which received the preparation containing the base plus 25% finely powdered salt was 0.75 i.u./ml. at 36 hours. At 72 hours, two cows (40% of the group) were free of penicillin and the average penicillin level in the milk from the other 3 cows was 0.15 i.u./ml; at 84 hours 3 cows (60% of the group) were clear.

This Example illustrates the beneficial effect of adding finely powdered water-soluble material in a different type of base (the vegetable oil/Beeswax base).

EXAMPLE 3

A further base comprising 80% arachis oil and 20% oil of theobroma was made. One part by weight of this base and one part by weight of finely powdered sodium chloride as used in the previous Examples were mixed together and sodium benzyl-penicillin added to 100,000 i.u. /dose of 4 grams.

As in the previous Examples a group of 5 cows was treated, one dose per quarter of each cow. In 24 hours, average penicillin levels in the milk had fallen to approximately 1.0 i.u./ml; in 36 hours 3 of the 5 cows were completely free of penicillin in the milk and in 48 hours all 5 cows were clear.

This Example illustrates the effect of finely powdered water-soluble material in a third type of base, and also illustrates the greater speed of release obtainable with a higher concentration of such material.

EXAMPLE 4

The base of Example 1 was again taken, and 3 parts were mixed with 1 part of coarse particulate sodium chloride. The particles were sieved to remove fine powder and only particles greater than 150 microns in diameter were used. The particles used varied from about 150—500 microns. Benzyl-penicillin to 100,000 i.u./dose of 4 grams was added and the preparation was used to treat a group of 5 cows as before.

At 36 hours the average level of penicillin in the milk was 0.7 i.u./ml. At 72 hours although one cow was substantially free from penicillin in the milk. The remaining 4 cows had an average level of 0.1 i.u./ml. and even at 108 hours only 3 cows were clear, the other 2 still having a level of 0.1 i.u./ml.

Thus again 120 hours or more were required to bring all cows to the point of substantial freedom from penicillin in the milk, as was the case when this base was used alone without added salt in Example 1.

This Example illustrates the importance of the powdered water-soluble material being finely powdered. Practically no effect is obtained with an equivalent quantity of the same material in a coarse powder form.

While the invention is of particular importance in relation to compositions intended for the veterinary use described above, it can also be employed in connection with other compositions which are used to give controlled release of an antibiotic, or other medicament from an oily base.

WHAT WE CLAIM IS:—

1. Compositions comprising a therapeutic agent in a hydrophobic viscous or gel base, and comprising in addition at least 10% by weight of a solid, finely divided physiologically innocuous non-gelling water-soluble compound of average particle size below 150 microns.

2. Composition suitable for use in the treatment of mastitis and related infections in animals, which comprise an antibiotic, a hydrophobic viscous or gel base, and in addition at least 10% by weight of a solid, finely divided physiologically innocuous non-gelling water-soluble compound of average particle size below 150 microns which, in the concentration in which it will be contained in the milk, is substantially without therapeutic action in said infections.

3. Compositions according to claim 2, in which the additional water-soluble compound is at least 0.1% by weight in milk at 37° C.

4. Compositions accordings to any one of the preceding claims, in which the maximum particle size of the additional water-soluble compound is below 50 microns and the average particle size is at most 20 microns.

5. Compositions according to any one of the preceding claims, in which the proportion of the additional water-soluble compound is 25—50% by weight.

6. Compositions according to any one of the preceding claims, in which the additional water-soluble compound is sodium chloride or calcium lactate.

7. Compositions according to any one of claims 1—5, in which the additional water-soluble compound is a sugar.

8. Compositions according to any one of the preceding claims, containing more than one therapeutic agent.

9. Compositions according to any one of the preceding claims, in which the base is a mineral oil gelled with an aluminium soap.

10. Compositions according to claim 1 or 2 substantially as hereinbefore described.

11. Process for the treatment of mastitis and allied infections in cows, which comprises introducing into the udder of the cow a composition claimed in claim 2 or 3 or any one of claims 4—10 as appendant to claim 2.

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